Differences in Brain Activation Between Tremor- and Nontremor-Dominant Parkinson Disease

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Objective: To compare differences in functional brain activity between tremor- and nontremor-dominant subtypes of Parkinson disease (PD) using functional magnetic resonance imaging.

Design: In our study, patients with tremor-dominant PD and those with nontremor-dominant PD performed a grip task, and the results obtained were compared using voxelwise analysis. Areas of the brain that were significantly different were then examined using a region-of-interest analysis to compare these patients with healthy controls. Voxel-based morphometry was used to determine macroscopic differences in gray and white matter volume between patient groups.

Setting: University-affiliated research institution.

Participants: A total of 20 drug-naive patients with PD (10 with tremor-dominant PD and 10 with nontremor-dominant PD) and a total of 20 healthy controls.

Main Outcome Measures: Blood oxygenation level-dependent activation and percent signal change.

Results: Robust findings across both voxelwise and region-of-interest analyses showed that, compared with patients with tremor-dominant PD, patients with nontremor-dominant PD had reduced activation in the ipsilateral dorsolateral prefrontal cortex, the globus pallidus interna, and the globus pallidus externa. Region-of-interest analyses confirmed that patients with nontremor-dominant PD had reduced activity in the ipsilateral dorsolateral prefrontal cortex, the globus pallidus interna, and the globus pallidus externa compared with patients with tremor-dominant PD and healthy controls. Patients with tremor-dominant PD had increased activity in the contralateral dorsolateral prefrontal cortex compared with patients with nontremor-dominant PD and healthy controls. These results could not be explained by differences in gray or white matter volume.

Conclusions: Reduced brain activity occurs in the prefrontal cortex and globus pallidus of patients with nontremor-dominant PD compared with both patients with tremor-dominant PD and healthy controls, which suggests that functional magnetic resonance imaging is a promising technique to understand differences in brain activation between subtypes of PD.

basal ganglia, with patients with nontremor-dominant PD having reduced dopamine levels in the globus pallidus. Using in vivo functional magnetic resonance imaging (fMRI), Spraker et al found that, compared with healthy controls, drug-naive patients with PD have reduced activity in the thalamus, primary motor cortex, supplementary motor area, and in all nuclei of the basal ganglia. Prodoehl et al also found that fMRI activity in nuclei of the basal ganglia correlates with specific symptoms such as bradykinesia and tremor in drug-naive patients with PD. However, to date, no direct comparison of brain activation in drug-naive patients with PD who have the tremor-dominant phenotype vs those who have the nontremor-dominant phenotype has been performed. The present study was designed to examine functional and structural differences between drug-naive patients with nontremor-dominant PD and patients with tremor-dominant PD using fMRI and voxel-based morphometry. We hypothesized that patients with nontremor-dominant PD would show both cortical and basal ganglia activation deficits compared with patients with tremor-dominant PD. We further test the hypothesis that areas that show reduced activation in patients with nontremor-dominant PD relative to patients with tremor-dominant PD will also show reduced activation in patients with nontremor-dominant PD relative to healthy controls.

### METHODS

A total of 20 drug-naive patients with PD who have never been treated with dopaminergic medications participated in the study (Table 1). The Mini-Mental State Examination score was greater than 26 for each participant. All patients were diagnosed with PD by a movement disorder neurologist and met the UK Parkinson’s Disease Society Brain Bank diagnostic criteria. A group diagnosis approach was used such that the diagnosis of each patient was confirmed by 7 other movement disorder neurologists (who looked at videotapes of the patients) in practice at Rush University Medical Center in Chicago, Illinois. Of these 20 patients, 10 were in the tremor-dominant group, and 10 were in the nontremor-dominant group. The criterion for inclusion in the tremor-dominant group was the presence of a tremor at rest in either the head-neck region or in at least 1 upper or lower extremity that was given a score of 2 from the motor examination section of the Unified Parkinson’s Disease Rating Scale (UPDRS). The criterion for inclusion in the nontremor-dominant group was the absence of a tremor at rest in the head-neck region or in any upper extremity. The diagnoses of all the patients were reconfirmed 2 years after MRI testing by reviewing the patients’ medical records, which were documented by the movement disorder neurologists. A consistent diagnosis was maintained over 2 years for each patient. Two years following testing, all but 3 patients with PD (1 patient with nontremor-dominant PD and 2 patients with tremor-dominant PD) had started either dopamine agonists or le-
gap). The functional magnetic resonance imaging experiment was a block-design paradigm of four 30-second task blocks and five 30-second rest blocks. During rest blocks, the participants fixated on a stationary red target without producing force. During task blocks, the participants performed 2-second pulse-hold contractions followed by 1 second of rest. The target bar represented 15% of the maximum voluntary contraction (MVC). A white cursor on the screen moved vertically and was related to the force produced by the participant.

The grip task consisted of each participant applying force to a fiber-optic force transducer (Aither Engineering), with patients using their most affected hand and controls using the hand that allowed us to maintain a similar left hand to right hand dominance ratio as the patient groups (Figure 1A). Images were collected using a quadrature volume head coil inside a 3-T MR scanner (GE Healthcare 3T94 Excite 2.0). Each participant’s head was stabilized using adjustable padding. The functional images were obtained using a T2*-sensitive, single-shot, gradient-echo planar pulse sequence (echo time, 25 milliseconds; repetition time, 2,500 milliseconds; flip angle, 90°; field of view, 200 mm²; imaging matrix, 64 × 64; 42 axial slices at 3 mm thickness; 0-mm gap). The anatomical images were obtained using a T1-weighted, fast spoiled gradient-echo pulse sequence (echo time, 1.98 milliseconds; repetition time, 9 milliseconds; flip angle, 25°; field of view, 240 mm²; imaging matrix, 256 × 256; 120 axial slices at 1.5 mm thickness; 0-mm gap).

The fMRI methods are consistent with previous work.10,11 The fMRI experiment was a block-design paradigm of four 30-second task blocks and five 30-second rest blocks. During rest blocks, the participants fixated on a stationary red target with- vodopa, and each of these patients had a positive response to drug therapy. Twenty healthy aged-matched controls also participated in our study (mean age, 58 years; 10 men and 10 women). The controls were healthy volunteers from the Chicagoland area who did not have a prior history of neurological or psychiatric disease. The UPDRS motor scores for all controls were 0. The first patient was enrolled on March 22, 2007, and the last patient was enrolled on October 2, 2010. The first healthy control was enrolled on May 7, 2007, and the last healthy control was enrolled in October 19, 2010. All participants provided written informed consent consistent with the Declaration of Helsinki, which was approved by the institutional review boards at Rush University Medical Center and the University of Illinois at Chicago.

After the force output data were collected, 4 points were marked for each pulse: onset of force, beginning and end of the sustained force period, and offset of force.14 Based on these marked points, 4 force variables were calculated: (1) mean force amplitude, (2) duration of force, (3) rate of change of increasing force, and (4) rate of change of decreasing force. Force data were analyzed in order to compare behavioral performance between groups. The difference in the group mean values was analyzed using a 1-way between-subjects analysis of variance for each dependent measure. All tests were evaluated as significant at P < .05.

AFNI, the public domain software (http://afni.nimh.nih.gov/afni/), was used to analyze fMRI data. Before analysis, fMRI data were transposed for those participants who used their left hand, so that the left and right hemispheres in all data sets were contralateral and ipsilateral to the tested hand, respectively. Head motion was less than 1 mm in x, y, and z directions for all participants. A voxelwise analysis was performed on the fMRI data to identify group differences in blood oxygenation level-dependent (BOLD) activation between the nontremor- and tremor-dominant patient groups. Motion-corrected individual data sets were normalized by dividing the instantaneous signal in each voxel at each point in the time series by the mean signal in that voxel across the scan. A Gaussian filter was applied to the resultant data sets (full-width at half-maximum, 3.3 mm). Then, the time series data were regressed to a simulated hemodynamic response function for the task sequence. Before group analysis, each participant’s anatomical and functional data set was transformed to standardized space using the normalized anatomical data set as a template. The output data for the tasks were analyzed using a mixed-effects, 2-way analysis of covariance with patient group (patients with tremor-dominant PD and those with nontremor-dominant PD) as the fixed factor and participant as the random factor. We analyzed the tremor-dominant vs nontremor-dominant comparison with and without covariates. We included action tremor scores from Table 1 as one covariate and bradykinesia minus tremor at rest as the other covariate. For the bradykinesia covariate, we summed bradykinesia items from the UPDRS (questions 23, 24, 25, 26, 29, and 31) and subtracted summed tremor at rest (question 20) values for both tremor- and nontremor-dominant groups. Adding the covariates to the model did not alter the findings, and the same areas were identified using either approach. Following the analysis of covariance, this yielded the estimated difference in the patient group mean values for task minus rest. These data were corrected for type I error using a Monte Carlo simulation model (AFNI, Alphasim). Data sets were thresholded at t < 3.8 (P < .005) with a minimum activation cluster volume of 205 μL (P < .05, corrected). Because nuclei in the basal ganglia are small, an uncorrected threshold of t < 3.8 (P < .005) was used.

Brain regions with activation differences between the nontremor- and tremor-dominant groups were compared with the brain regions of healthy controls using a region-of-interest analysis. Percent signal change (PSC) data were acquired, consistent with previous work.10 The regions of interest were determined based on the voxelwise analysis. One-way analyses of variance were performed to compare PSCs within regions of interest in patients with tremor-dominant PD, patients with non-
tremor-dominant PD, and healthy controls. Significant main effects were examined using Tukey honestly significant difference post hoc tests.

To ensure that any differences in voxelwise functional activation between nontremor- and tremor-dominant patients with PD were not due to changes in brain structure between patient groups, voxel-based morphometry analyses were implemented using SPM8 in MATLAB version 7.10 (The MathWorks Inc) and FreeSurfer version 5.0.0 (http://surfer.nmr.mgh.harvard.edu). The New Segment procedure described in the SPM8 manual, with enhanced preprocessing methods and modeling parameters based on the voxel-based morphometry study of Pereira et al, was used as the model for analysis. A voxelwise statistical analysis was performed by implementing the general linear model with comparison between the tremor- and nontremor-dominant groups using a 2-sample t test. Areas of volumetric variation had to meet a statistical threshold of $P < .05$, corrected for multiple comparisons using the false discovery rate method, and a minimum cluster size of 10 voxels.

Table 1 shows the characteristics of patients from both groups. There were no significant differences between patient groups with regard to age ($t_{39} = 0.91, P = .37$) or UPDRS motor score ($t_{39} = 1.03, P = .32$). Figure 1B shows a force trace from representative patients with PD from the tremor-dominant (left) and nontremor-dominant (right) groups. Despite having a visible tremor at rest, the patient with tremor-dominant PD was able to perform the task as well as the patient with nontremor-dominant PD. At the group level, the results of a 1-way analysis of variance showed no differences among nontremor-dominant, tremor-dominant, and control groups with regard to mean force ($F_{2,37} = 3.21, P = .07$), rate of change of increasing force ($F_{2,37} = 1.01, P = .36$), or rate of change of decreasing force ($F_{2,37} = 0.97, P = .39$). There was a main group effect for duration of force ($F_{2,37} = 5.22, P = .010$). Post hoc tests revealed that this was due to the longer duration of force in the tremor-dominant group compared with controls ($P < .013$), but there was no significant difference between nontremor- and tremor-dominant groups. Overall, these data suggest that behavioral performance is not driving any differences observed in the fMRI data.

Voxelwise analysis of the BOLD signal revealed reduced activation in the nontremor-dominant group compared with the tremor-dominant group in several cortical and subcortical areas: the bilateral dorsolateral prefrontal cortex (DLPFC), the contralateral pre-supplementary motor area, the ipsilateral inferior parietal lobule, the ipsilateral precuneus, the contralateral lingual gyrus, the contralateral caudate, the contralateral globus pallidus interna (GPI), the contralateral globus pallidus externa (GPe), and the ipsilateral thalamus (Table 2, Table 2. Talairach Coordinates for Significant Regions in Voxelwise Comparison Between Patients With Tremor-Dominant PD and Those With Nontremor-Dominant PD

Table 2 shows the results of voxelwise comparison between nontremor- and tremor-dominant groups that could have accounted for the between-group differences found in the functional voxelwise analysis. An uncorrected threshold at $P < .001$ did not reveal any differences between groups for the regions shown in Table 2.

Follow-up region-of-interest analysis of the areas listed in Table 2 confirmed findings from the voxelwise analysis for the nontremor- and tremor-dominant comparison in the bilateral DLPFC, the contralateral GPI and GPe, the ipsilateral thalamus, the inferior parietal lobule, and the precuneus (Table 3). In each of these areas, the PSC was lower in patients with nontremor-dominant PD than in patients with tremor-dominant PD. Patients with nontremor-dominant PD showed lower PSCs in the ipsilateral DLPFC, the GPI, and the GPe than did controls (Figure 2C). Patients with tremor-dominant PD were only different from controls in 1 area, the contralateral DLPFC, where the PSC was higher in patients with tremor-dominant PD than in controls (Figure 2C, Table 3). Thus, the bilateral DLPFC, the contralateral GPI and GPe, the ipsilateral thalamus, the inferior parietal lobule, and the precuneus are areas that show robust differences between tremor- and nontremor-dominant patient groups across both voxelwise and region-of-interest analyses.

The present study examined functional and structural differences in the brains of drug-naïve patients with either tremor- or nontremor-dominant PD, using fMRI and voxel-based morphometry. Follow-up analysis using a region-of-interest approach was performed to confirm between-group differences and to examine how these between-group differences related to a healthy control group. Robust findings across both analysis methods showed significant differences both cortically (prefrontal cortex) and subcortically (globus pallidus) between patients with nontremor-dominant PD and patients with...
in patients with non-tremor-dominant PD also had lower PSCs in the ipsilateral DLPFC compared with controls. One possibility is that the presence of resting tremors in the tremor-dominant group could not explain these findings because increased resting activity in the tremor-dominant group could reduce the task-related BOLD signal change in the tremor-dominant group, thus minimizing any between-group differences. Another possibility is that DLPFC activity was higher in the tremor-dominant group to suppress tremor because the DLPFC has been related to inhibiting force output.\(^4\) We compared the BOLD activity with and without covariates that included action tremor and bradykinesia minus resting tremor, and the findings were similar for the DLPFC and all other areas with and without the covariates. Thus, although the presence of a tremor at rest in the tremor-dominant group and the absence of a tremor at rest in the non-tremor-dominant group led to between-group differences in the BOLD signal, these group findings are robust to the UPDRS scores as covariates.

A prior postmortem analysis\(^2\) of brain structure in PD has shown a significantly higher mean overall Lewy body score for patients with non-tremor-dominant PD than for patients with tremor-dominant PD, particularly in the prefrontal regions of the cortex. Patients with non-tremor-dominant PD show signs of bradykinesia more frequently than patients with tremor-dominant PD, and they also show minimal tremor at disease onset.\(^7\) It is not clear whether this is due to pathological differences in brain structure between phenotypes at the outset of the disease or whether this is due to adaptive changes from symptom differences between phenotypes. To resolve this question, it would be necessary to perform correlational analyses between Lewy body deposition and measurements of bradykinesia. Nevertheless, brain changes observed postmortem seem to support clinical subtyping of patients into either non-tremor- or tremor-dominant PD phenotypes. Because the present study examined tremor- and non-tremor-dominant patients relatively early in the disease process, prior to starting dopaminergic medication, our findings suggest that grouping patients into tremor- and non-tremor-dominant groups based on motoric features reveals changes in the BOLD signal in areas such as the DLPFC. Whether these changes in the BOLD signal in the DLPFC have any relation to cortical Lewy body deposition is beyond the scope of the present study, and caution should be taken in attempting to relate these findings without further inquiry.

The task used in the present study was chosen because it requires robust activation of frontal cortical regions and parietal cortical regions, including the primary motor cortex, the dorsal and ventral premotor cortices, the supplementary motor area, the DLPFC, the inferior parietal lobule, the superior parietal lobule, and the anterior cingulate cortex.\(^17,18\) However, in the present study, only the DLPFC in the prefrontal cortex was different between patient groups in both voxelwise and region-of-interest analysis, which suggests that this prefrontal area is robustly sensitive to differences in patients clustered into tremor- and non-tremor-dominant groups. The DLPFC has been suggested to play an important role in working memory and executive func-
tion. Indeed, the DLPFC activation has previously been shown to be sensitive to changes in learning in early-stage PD, with activation being normal at baseline but decreasing to subnormal levels after 2 years.19 Kikuchi et al20 used single-photon emission computed tomography to show hypoperfusion in the DLPFC, the supplementary motor area, and the insular cortex in PD. However, only hypoperfusion in the DLPFC and the insular cortex was correlated with disease severity, leading Kikuchi et al20 to suggest that the DLPFC and the insular cortex may play key roles in specific symptoms of impairment at advanced stages, such as impaired working memory, postural instability, and autonomic dysfunction. The results of the present study suggest that disease severity alone may not be the main feature of this difference and that symptom-specific differences could be another factor that should be considered. That is, patients with a nontremor-dominant subtype of PD, even in the earliest stages of the disease, may show greater deficits in frontal cortical areas compared with patients with a tremor-dominant subtype.

Subcortically, the present study showed reduced BOLD activity in the GPi, the GPe, and the thalamus in patients with nontremor-dominant PD compared with patients with tremor-dominant PD (Tables 2 and 3). Because the basal ganglia have established connections with the DLPFC, it could be that the cortical findings are due to changes in the basal ganglia, or it could be that these cortical and subcortical findings are not directly related. The reduced activity in the GPi in the nontremor-dominant group was in the ventral part of the GPi, and this location and pattern of findings for the BOLD signal are consistent with previous postmortem findings of reduced dopamine levels in the ventral part of the GPi in patients with nontremor-dominant PD compared with patients with tremor-dominant PD.9 It is also consistent with the previous finding of Prodoehl et al11 in which a group of drug-naive patients with PD with a mixed phenotype had higher tremor scores on the UPDRS that were associated with higher PSCs in the GPi. In this study,11 there was a negative correlation between disease severity and PSC in all other nuclei of the basal ganglia and in the thalamus, and bradykinesia was the symptom that most consistently predicted BOLD activation in these regions. In a different study,21 patients with moderate PD were tested following a 12-hour withdrawal from medication, and it was found that pallidal dopamine depletion correlated with clinical tremor severity and that the GPi, the GPe, and the putamen were transiently active during the onset of tremor episodes. Our findings extend this work by showing that early-stage, drug-naive patients clustered into a nontremor-dominant group had reduced BOLD signals in specific nuclei of the basal ganglia (the GPi and GPe) and in the thalamus compared with early-stage, drug-naive patients clustered into a tremor-dominant group. Furthermore, our findings suggest that group differences in basal ganglia activation between patients with PD and healthy controls may be driven in part by patients with motoric features consistent with the nontremor-dominant group rather than the tremor-dominant group.

Comparing patients with PD with healthy controls, we found that only one area in the region-of-interest analysis showed significantly increased activation in PD. The contralateral DLPFC showed a significantly greater PSC in patients with tremor-dominant PD compared with controls. Although a tremor at rest in PD has been associated with increased metabolism in the thalamus, substantia nigra,pons, and premotor-cortical network, suggesting an increased functional activity of thalamo-motor projections,22 what underlies increased DLPFC activation in patients with tremor-dominant PD deserves further study. In addition, the future study of symptom-specific differences in patients with a more advanced stage of the disease should examine cognitive changes that might accompany the functional activation deficits found in the present study. Because the patients included in our study were drug-naive patients, it could be argued that patients with atypical parkinsonism were included, particularly in the nontremor-dominant group. To minimize this possibility, reconfirmation of the diagnosis was made 2 years after MRI testing was performed. Also, after 2 years, all but

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<th>P Value</th>
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<th>Controls vs TD</th>
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Abbreviations: ANOVA, analysis of variance; DLPFC, dorsolateral prefrontal cortex; GPe, globus pallidus externa; GPi, globus pallidus interna; IPL, inferior parietal lobule; NTD, patients with nontremor-dominant Parkinson disease; SMA, supplementary motor area; TD, patients with tremor-dominant Parkinson disease.

* Determined by use of the Tukey honestly significant difference post hoc test.
3 patients had started dopamine therapy, and each of the other 17 patients responded positively to medication, which gave us confidence in the findings.

In conclusion, the present study confirmed that functional differences in the basal ganglia and cortex between patients with PD and healthy controls are primarily due to patients with the non-tremor-dominant subtype of PD rather than the tremor-dominant subtype. These findings suggest that objective measures of brain function may be useful in future genotype-phenotype analyses and in targeted therapeutic trials focused on PD subtypes.

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